SUMMARY
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Viral Hemorrhagic Fevers

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***Please note:** Data and analysis discussed in these presentations were current when presented. Data collection and analysis are ongoing in many cases, therefore updates may be forthcoming elsewhere on this website, through publications such as CDC's Morbidity and Mortality Weekly Report or other venues. Presentations themselves will not be updated. Please bear this in mind when citing data from these presentations.*

OVERVIEW

Viral hemorrhagic fevers (VHFs) is a description of a syndrome, but it doesn't stand alone as one specific thing. It's a mixed bag of several different diseases, which have different requirements for things like:

- Treatment,
- Supportive care
- Infection control

Viral hemorrhagic fevers represents a group of infections that start as an acute infection. This includes; fever, muscle aches, malaise and ultimately prostration, meaning you're very sick and can hardly get up. There's multi-system compromise, in other words, many different organ systems are involved. Hemorrhages themselves may be actually somewhat small in volume. People discuss hemorrhagic fevers as though there are large quantities of blood involved and that's not always the case. There's a very poor prognosis associated with patients who have shock, encephalopathy, or extensive hemorrhage.

Viral hemorrhagic fever viruses:

• Filoviruses	Ebola hemorrhagic fever (EHF) Marburg virus
• Bunyaviruses	Rift Valley fever (RVF) Crimean Congo Hemorrhagic Fever (CCHF)
• Arenaviruses	Lassa Fever "New World Arenaviruses"

DIFFERENTIAL DIAGNOSIS

Differential diagnosis needs to be considered when looking at VHFs. The virus occurs in places that have many standard tropical illnesses, especially malaria and typhoid fever. In addition, places where those VHFs show up, there seems to be a high prevalence of bacterial gastroenteritis and Rickettsial diseases. Even common illnesses that are vaccine preventable may also be prevalent in these places (e.g., things as common as measles can show up as an acute febrile illness and look somewhat like a viral hemorrhagic fever.)

LABORATORY DIAGNOSIS

- Malaria smears
- Blood cultures (closed system)
- CBC, especially platelet count
- Transaminases (prognostic value, patients with high elevated transaminase values tend to have a much poorer prognosis)

DESCRIPTION OF THE VIRUSES

These viruses are encapsulated single stranded RNA viruses. They all create a similar syndrome, although in the actual mechanisms whereby the syndrome is caused, the pathogenesis might be different. They tend to persist in nature in reservoirs such as rodents, bats and even mosquitoes. Geographically, those host populations are part of what keeps them restricted to one particular area. If the host rodent or the host bat is restricted to one particular geographic area, then the virus is restricted there as well.

Filovirus

- Ebola
  - Zaire
  - Sudan
- Marburg

Outbreaks

- 1967, Marburg, Frankfurt, and Belgrade
- 1975, Zimbabwe
- 1980, N.W. Kenya
- 1987, W. Kenya
- 1998-2000, N.E. Democratic Republic of Congo

Ebola

- 1-2 week incubation
- Abrupt onset fever, headache, myalgia
- GI symptoms, chest pain, delirium
- 53-88% case-fatality
- ~ 45% hemorrhage
- Person-to-person transmission
- African Rain Forest
- Unknown reservoir

Bunyaviruses

Rift Valley fever

- Affects sheep and cattle
- Mosquito borne
- Could cause a great deal of economic and agricultural impact if it entered our country
- Asymptomatic or mild illness
- On rare occasions, it could cause a viral hemorrhagic fever that includes encephalitis and even retinitis
- Has been transmission to human by laboratory aerosols
- 1% overall mortality
- Ribavirin therapy is questionable because of clinical trial suggesting greater risk of encephalitis among people who receive the treatment
- Live attenuated vaccine undergoing trials, but not available in the U.S.

Clinical features of Rift Valley fever

- 3-7 day incubation, 3-5 day duration
- Asymptomatic or mild illness
- Fever, myalgia, weakness, weight loss
- Photophobia, conjunctivitis
- Encephalitis
- <5% hemorrhagic fever
- 1-10% vision loss (retinal hemorrhage, vasculitis)

Crimean-Congo hemorrhagic fever (CCHF)

- Very widely distributed infection
- Transmission is through ticks and contact with infected blood from sick animals or animal products
- Person-to-person transmission has occurred due to contact with infectious body fluids in the hospital setting
- Total mortality for CCHF is 15% to 40%
- Effective therapy is available in the form of ribavirin
- CCHF shown to occur in large parts of Asia, as well as the former Soviet Union, the Arabian Peninsula, and parts of Central, South and West Africa

Clinical features of CCHF

- 4-12-day incubation period following exposure to an infectious tick
- Incubation period as short as 2-7 days if there is direct contact with infectious body fluids
- Illness begins with a sudden onset of fever and chills (including muscle aches and a severe headache)
- Malaise, gastrointestinal symptoms and anorexia
- Laboratory examination shows leukopenia, thrombocytopenia and hemoconcentration with proteinuria on urinary exam, and elevated liver transaminases, in particular AST
- Hemorrhaging may be profuse with very large bruises and ecchymoses being most common

Preventing CCHF

- Use DEET-containing insect repellents on the skin, as well as permethrin-containing repellants for clothing
- Remove ticks on a regular basis, at least twice a day
- If a tick is attached, it's important not to crush or otherwise damage the tick, but to carefully remove the tick by grasping its mouth parts just at the level of the skin and pulling gently and steadily directly away from the skin
- Livestock hygiene; animal pens can be a source of infection. (There has been documentation of cases where an infected flock has moved through a holding pen and then an uninfected flock inhabiting that pen, even very briefly, can become infected)

Pathogenesis (CCHF)

- Viremia present throughout disease
- Immunofluorescent antibody test becomes positive in patients destined to survive days 4-6, often simultaneously with viremia
- Recovery may be due to CMI or neutralizing antibodies
- Patients that die are usually still viremic
- Virus grows in macrophages and other cells
- DIC often present
- Poor prognosis signaled by early elevated AST and clotting

Slaughterhouses

- Sheep and cattle who are infected don't necessarily have symptoms
- Infected sheep and cattle can transmit to humans by having contact with blood and fresh tissues

Arenaviruses

There are two categories of Arenaviruses. The New World viruses are present in South America, whereas Old World is restricted to Africa

- Old World refers to Lassa fever virus
- New World Arenaviruses, include Junin, Machupo, Guanarito, and Sabia

Old World Lassa fever

- Found in West Africa
- Disease maintained and transmitted by a rodent of the Mastomys natalensis complex.
- Person-to-person transmission related to direct contact, sexual contact and breast-feeding
- Rodent related transmission occurs when infected rodents either contaminate food supplies through urine and other secretions, or if there is contact with infectious urine directly
- Mortality among Lassa fever patients is only about 1% to 3% (However, it becomes higher among patients who are sick enough to be hospitalized and the hospital figure is more like 20%)
- Effective therapy in the form of ribavirin is available
- Eighty percent of Lassa fever patients are asymptomatic (This is why there's such a difference between mortality among the general population versus the hospitalized population)
- Among people who do have symptoms, the symptoms include fever, chest pain, a sore throat, muscle aches, headaches, abdominal pain, vomiting and there can be a lot of swelling and puffiness around the face and eyes
- Mucosal bleeding is fairly common, especially of the gums, and proteinuria is seen in the urine. In addition, sensory neuro hearing loss is seen in about 25% of Lassa fever patients and this may last after the resolution of the rest of the disease.
- Spontaneous abortions are also known to occur

New World arenaviruses

- Distribution mostly in South America, but also in North America
- All are carried among rodent hosts except for the Tacaribe virus, which is carried and transmitted by a bat
- All of the viruses are consistent in their spread in that if human populations disturb an ecosystem, for example, by clear-cutting a forest and planting sugar cane, there's a tendency for native rodents to move from the disturbed ecosystem into places where food and shelter are available, such as a human habitation nearby the field

Junin virus

- Found in Argentina
- Accociated with the autumn grain harvest when humans have more contact with the culprit rodent
- Person-to-person transmission doesn't seem to happen very often, although at least one instance of sexual transmission has been documented from an infected person to someone else
- Mortality of this disease is about 15% to 20%
- At least in Argentina, immune plasma has been tried with some success
- The effectiveness of ribavirin remains unclear

Machupo, also known as Bolivian hemorrhagic fever

- Has been identified in the El Beni department of Bolivia, and is also carried by rodents
- Some evidence of person-to-person transmission among sick individuals in healthcare facilities – mortality with this disease is about 20%
- Therapeutic efficacy of ribavirin remains unclear

Guanarito virus, also known as Venezuelan hemorrhagic fever

- Occurs in Venezuela
- Carried by a rodent
- Person-to-person transmission has not been seen with this disease – mortality is about 20-30%
- Efficacy of ribavirin here is not clear

South American hemorrhagic fevers

- 1-2 week incubation
- Gradual onset of fever, malaise, myalgia, and anorexia
- Headache and abdominal pain, nausea, vomiting, and lightheadedness
- Hemorrhagic features include petechiae, especially in the armpits and on the palette, as well as bleeding gums
- Neurologic signs (including lack of reflexes and tremor)
- Leukopenia, thrombocytopenia and proteinuria can be seen on laboratory examination
- 70% get better without any treatment after about a week, although many people report that they remain weak and tired for quite some time
- Among the other 30%, there can be severe disease with hemorrhages, more severe neurologic syndromes, and in very severe cases, both (The latter category is associated with a very high mortality)

Treatment (General VHF)

- Supportive therapy; sedation and analgesia
- Treatable illnesses that can act as though they might be VHFs need to be diagnosed and treated promptly (These diseases sound similar at the beginning with basically a flu-like illness possibly with some neurologic features)
- All of the symptoms can be true for things like malaria, leptospirosis, typhoid and so on, so it's very important that those be ruled out and treated promptly
- Hydration is something that can be provided, but this has to be done with a great deal of care since, in terms of pathophysiology, especially with Ebola, the leakage also involves the lungs, and can lead to congestive heart failure very quickly
- Experience with pressor and cardiotonic drugs is limited
- If possible, support coagulation system – and provide appropriate transfusions

Ribavirin

- Nucleoside analog antiviral drug that blocks an enzyme called IMP dehydrogenase
- Licensed in the U.S. from treatment of RSV (Respiratory Syncytial Virus and Hepatitis C virus). However it is not licensed for VHF treatment, although protocols are currently being developed for contingency use
- Some potential adverse effects with this drug including dose-dependent reversible anemia, and acute pancreatitis
- In rodents, the drug is known to be teratogenic

Indications for Ribavirin (Copegus, Rebetol, Virazole)

- Filoviruses No
- Rift Valley No
- CCHF Yes
- Lassa Yes

- Argentine HF Yes
- Other New World Arena Maybe

Toxicities
- Teratogenic
- Extravascular hemolysis
- Bone marrow suppression
- Rigors with abrupt IV administration
- Reversible hyperbilirubinemia, hyperuricemia with oral administration
- Itchiness, nausea, depression, cough

INFECTION CONTROL

At the CDC, viruses that cause viral hemorrhagic fevers are handled in a bio-safety level four laboratory. This is very different from the level of protection that's required when we're taking care of living patients. As long as we're not using a mechanical device on a patient, whether that's a respiratory suction device or whatever else that might create an aerosol, then the following precautions are appropriate.

Given that we don't have vaccines for these viruses and that treatment options are very limited, one of the **most important things to do is not spread it around**.

Standard precautions

Standard precautions involve the constant use of gloves any time you think you're going to touch something that's bloody, moist, or involves broken skin or mucus membranes. When you're done, you take them off and you wash your hands with soap and water.

Likewise, if you think you might get splashed or get something on you, we put on a gown, a mask, or a face shield to prevent splashing. We never know whether or not what we're touching is infectious, so this constant level of protection is the baseline that's provided by standard precautions.

Transmission based precautions
- Airborne
- Droplet
- Contact

For VHFs, the transmission based precaturions that are required are droplet and contact precautions:
- We want to make sure that we contain any infectious blood or body fluids to one area, and we also want to make sure that there's no risk of splashing to our mucus membranes
- As part of standard precautions, there are basic things like appropriate sharps handling and disposal, waste handling, and laundry practices that are part of that process (These should always be applied to any patient care and are an important part of VHF management)

Droplet

Make sure that all of your mucus membranes are covered. People are very good about wearing masks, and in this case a mask can be a simple paper surgical mask. However, many times people forget to cover their eyes. This has been the source of transmission of Ebola during outbreaks when, despite the use of a mask, somebody was splashed with infectious blood to their conjunctiva, so it's important to cover all of those things.

In addition, it's important to remember (as we learned with SARS) that an infectious droplet, once it lands, can actually be reintroduced to your mucus membranes if you touch it with your

hands and then rub your eyes. Hand hygiene, which is part of standard precautions, is of incredible importance in many of these diseases, including those transmitted mostly by droplets.

Contact

Contact precautions are for diseases that create a contaminated environment that can be a source of infection. These are diseases like shigella dysentery where the entire environment might be contaminated by infectious material, on bed-rails, tabletops and so on. In this instance, we put on protective equipment like gowns and gloves before going into a room. Then we remove that equipment when we're done working, leave it in the room in an appropriate receptacle, exit the room and wash our hands immediately; the point being to contain infectious material in one room.

For casual contacts, somebody who shared an airplane ride or a hotel, but other wise did not have direct contact with an ill individual, there's no surveillance indicated. These people are not considered to be at risk. For close contact, somebody who had direct contact with a patient, that is touching or direct contact with body fluids during the symptomatic illness, these people deserve to be watched very closely for the entire incubation period of the suspected disease to make sure that they don't develop a fever. If they do develop a fever, they need be brought in for assessment and possibly isolation. For high-risk contacts, these are people who have needle stick injuries, who have known mucosal exposure to body fluids or known sexual contact with somebody who is infectious, these people also need to be watched for fever, but they may benefit from inpatient observation just to be sure that they're followed up appropriately.

Airborne

There are some places where it's suggested that airborne precautions be used for VHF management. There is no human evidence of airborne transmission of VHF. There are a couple of monkey experiments whereby it's been shown that a tube attached to a monkey with aerosolized virus being pumped through it can result in the monkey becoming infected, and that's about all we have to suggest the possibility of airborne transmission. However, because of the severity of the disease and the fear that's often associated with it, many sources have decide to "up the ante" and suggest airborne precautions, but it's currently not based on clear evidence.

RELATIVE RISK OF TRANSMISSIBILITY

- None: Yellow fever, Dengue, Rift Valley fever, Kyasanur, Omsk (arboviruses), hanta viruses
- Low: Lassa and South American arenaviruses
- High: Ebola, Marburg, CCHF

For more information:
Complete text of the current CDC/HICPAC Isolation Precautions are available on-line.
www.cdc.gov/ncidod/hip/isolat/isolat.htm
www.cdc.gov/ncidod/dvrd/spb/index.htm
http://bt.cdc.gov/agent/vhf/index.asp

QUESTIONS AND ANSWERS

Q: Just a couple questions in the management of Lassa fever. Do you have any recommendations as far as what level of respiratory protection [there should be] for healthcare workers? And would you recommend adding bleach to the toilets with an admitted patient?

A: For Lassa fever, and if you're just doing basic patient care, then droplet precautions is perfectly adequate. There's not a need for high-level respiratory protection. On the other hand, if you're processing specimens or cleaning a space that might be contaminated with rodent urine, then higher-level protection might be warranted. In terms of bleach in the toilet, I would not routinely do that. There wouldn't be a clear reason for doing that, assuming you have normal toilet facilities. Diluted bleach can be a useful way to

clean surfaces, but there are also many different EPA registered hospital disinfectants that work well, as well. Because all of these viruses are enveloped, they tend to be very easily destroyed by detergents and similar products. So, doing things like putting bleach in the toilets is not necessary. In terms of infectious material going down the toilet and into the sewage system, that's not considered a risk since we routinely allow many things to go down our sanitary sewer systems and the combination of sewage treatment and dilution and so on prevents that from being a source of environmental transmission.

Q: Dr. Bell, thank you so much for that very informative presentation. I wanted to know if we know exactly what causes the hemorrhage and why we only see it in less than half the cases of VHF?

A: Well, it's less than half the cases of Ebola, specifically, if you use that number, but the cause of the hemorrhage is several-fold. Part of it is the increased capillary permeability that can promote petechiae and bruising and so on. There's also platelet dysfunction. Then in addition to that, certainly with Ebola, there's direct damage to liver tissue. Synthesis of clotting factors can also be reduced so that you have a multiple reasons for hemorrhage.

Q: I was surprised to see VHFs listed as a Category A. I thought maybe you could expand on that just a little bit for us.

A: When you say Category A, do you mean the BT threat agent?

Q: Exactly. I know it was important to ensure that we had some background in education on all of the Category A agents, and I did expect to see anthrax, botulism, plague, and small pox, but when I saw VHFs, to be honest with you, I was surprised. I wondered what more we should know from that perspective.

A: This is reflective of the source of some of these lists and the types of considerations that have gone into this. The fact that VHFs, per se, has been put on a threat agent list is kind of silly, because we just talked about a whole range of diseases that have a very different degree of severity, a different degree of transmissibility. It's kind of nonsensical to put "VHF" on a list of threat agents.

However, because people tend to think of Ebola specifically when they talk about VHFs, because the word hemorrhage is kind of scary, and because of the sort of sensationalistic ideas that some folks have about what these diseases look like, I think the fear, in and of itself, was probably a reason for including it. Also, the fact that (at least with Ebola), there's very efficient person-to-person transmission. If it did arrive here, it's possible that there could be at least some secondary cases. Realistically, do I think that there would be rampant spread of Ebola or similar viruses within our population? I think that by adhering to careful infection control precautions that we use in our hospitals as a standard of care in this country, I think we would be very capable of appropriately caring for patients and preventing secondary spread. The key would be to identify such patients early and make sure that they were brought to good care.

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Please send any questions you many have to coca@cdc.gov or you can contact the CIL, the clinician information line, at 877.554.4625. And thank you to Dr. Bell for this wonderful presentation on viral hemorrhagic fevers.